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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/945,166	08/31/2001	David R. Elmaleh	FLA-003.01	1584

25181 7590 03/03/2009

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
03/03/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/945,166	ELMALEH ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-8,10,25-27 and 30-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-8,10,25-27 and 30-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/26/08*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application

6)☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Claim interpretation

Claim 1 as amended recites that the oligonucleotide is designed to promote retention of the construct by a cell. Applicants point to page 18, lines 8-11, of the specification as providing support for this limitation. This page reads in part that "the nucleic acid portion of the subject constructs serves to augment the targeting moiety by selectively promoting retention of the construct by target cells which express a particular nucleic acid." Since this sentence relates the nucleic acid portion's ability to promote retention to the existence of a particular nucleic acid in a cell, this is interpreted to mean that the retention is a result of hybridization of the nucleic acid portion of the construct to the nucleic acid in a target cell. The specification provides no other description of any type of structural elements that can be designed into an oligonucleotide in order to provide the function of promoting retention of the construct. Therefore this limitation is limited to this single property, hybridization with a target nucleic acid, and any oligonucleotide construct in the prior art that hybridizes to a particular nucleic acid is considered to promote retention of a construct by a cell and satisfy this limitation.

Claim Rejections - 35 USC § 103

Claims 1, 5, 8, 10, 25-27 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuijpers et al. (EP 0 490 434, of record) in view of Priest (US 5,391,723), Gewirtz et al. (US 5,098,890, of record) and Low et al. (US 5,994,320, of record).

The claims are directed to targeted oligonucleotide constructs comprising a targeting moiety, an antisense oligonucleotide or oligonucleotide analog modified to enhance its efficacy, pharmacokinetic properties or physical properties and an imaging agent suitable for use in PET, SPECT or MRI. The oligonucleotide portion of the construct is an antisense specific for the C-myb, N-myc, C-myc or PSA genes. In specific embodiments, the imaging agent is a radiolabel, the construct further comprises a therapeutic agent and the antisense oligonucleotide portion of the construct comprises specific modifications.

Kuijpers et al. teach phosphorothioate antisense oligonucleotides conjugated with a radioisotope. Kuijpers et al. teach ^{123}I and ^{131}I as specific radioisotopes. These labeled oligonucleotides are disclosed as being useful for targeted therapy of tumors. Kuijpers et al. teach that the labeled oligonucleotide is targeted to a tumor cell by binding to an antibody oligonucleotide conjugate wherein the labeled oligonucleotide then enters the cell as a therapeutic agent (see scheme 1). Thus, Kuijpers et al. disclose a construct containing a targeting moiety that is an antibody, an oligonucleotide and an imaging agent suitable for use in PET, SPECT or MRI. The antisense oligonucleotide of Kuijpers et al. is a therapeutic agent that is derivatized with phosphorothioate, which increases nuclease resistance and is specific for mRNA,

meeting the limitations of claims 25-27 and 30-32. Although Kuijpers et al. is silent with regard to the ability of the disclosed constructs to cross the blood-brain barrier, because the constructs disclosed by Kuijpers et al. meet the structural limitations of the claims, they are assumed in the absence of evidence to the contrary to have essentially no ability to cross the blood-brain barrier. Kuijpers et al. do not teach constructs where all components are covalently linked and do not teach oligonucleotide constructs containing oligonucleotides that are antisense to C-myb, N-myc, C-myc or PSA genes.

At the time the invention was made, it was well known to those of ordinary skill in the art that antibody-oligonucleotide conjugates used in targeted therapy of tumors can be covalently linked. This knowledge is exemplified by Priest, who teaches such conjugates for use in delivering therapeutic agents.

Gewirtz et al. and Low et al. each teach antisense directed to C-myb. Gewirtz et al. teach (see abstract) that oligonucleotides targeted to C-myb are useful in treating hematologic neoplasms. Low et al. teach at column 1, line 15 through column 2, line 25 that C-myb is involved in cellular proliferation and differentiation and that antisense to C-myb is known to inhibit proliferation of several cell lines.

It would have been obvious to one of ordinary skill in the art to use the constructs taught by Kuijpers et al. as useful in targeting oligonucleotides to tumors in order to deliver a C-myb oligonucleotide to a tumor and would further be obvious to produce such a construct where all components are covalently linked. Because Kuijpers et al. teach a construct for targeting tumor cells and because Low et al. and Gewirtz et al. teach that C-myb is useful in treating cancers, one of ordinary skill in the art would have been motivated to target a C-myb antisense sequence to a tumor using the construct of

Kuijpers et al. in order to obtain enhanced delivery of the sequence to tumor cells. Based on the teachings of Priest of oligonucleotide-antibody conjugates that are covalently linked, one of ordinary skill in the art would recognize production of a covalently linked construct to be a matter of design choice. One of ordinary skill in the art would have had a reasonable expectation of success in making the construct of Kuijpers et al. with an antisense targeted to C-myb because Kuijpers et al. actually make their construct using techniques well-known in the art and Low et al. and Gewirtz et al. actually make antisense to C-myb using similar synthetic techniques.

Thus, the invention of claims 1, 5, 8, 10, 25-27 and 30-32 would have been obvious, as a whole, at the time of invention.

Response to Arguments

Applicants traverse the rejection over Kuijpers et al., Gewirtz et al. and Low et al. by arguing that Kuijpers' complexes do not promote retention of the construct by a cell.

This is unpersuasive because, as noted on the first page of the action, this limitation is considered to be satisfied by any oligonucleotide that hybridizes to a target nucleic acid.

Applicants traverse the combination of Kuijpers et al., Gewirtz et al. and Low et al. by arguing that the results described in example 6 of the specification are unexpected and that Gewirtz et al. and Low et al. neither teach nor suggest these unexpected results.

This is unpersuasive because the results that applicants assert are unexpected are not commensurate in scope with the claims. The claimed constructs have three

elements, an antisense oligonucleotide, an imaging agent and a targeting moiety selected from an antibody, a lectin, a ligand, a sugar, a steroid, a hormone, a nutrient, a small molecule and a protein. Example 6 describes the physical characteristics of constructs having only two of these elements, an antisense oligonucleotide and an imaging agent. Further, applicants assert the increased retention of an antisense oligonucleotide over a sense oligonucleotide is unexpected but do not relate this increased retention to the particulars of the claimed construct. In face, as noted above in the section describing claim interpretation, the instant specification explicitly relates a nucleic acid's ability to hybridize with a target with the promotion of retention. Therefore one would reasonably expect that any antisense oligonucleotide would have this characteristic.

New Claim Rejections - 35 USC § 103

Claims 1-3, 5-8, 10, 25-27 and 30-32 rejected under 35 U.S.C. 103(a) as being unpatentable over Kuijpers et al., Priest, Gewirtz et al. and Low et al. as applied to claim1, 5, 8, 10, 25-27 and 30-32 above, and further in view of Kayyem et al (US 6,232,295, of record).

Claims 1, 5, 8, 10, 25-27 and 30-32 are described in the preceding 103 rejection. Claims 2, 3, 6 and 7 recite particular types of imaging agents

The teachings of Kuijpers et al., Priest, Gewirtz et al. and Low et al. are described in the preceding 103 rejection. These references do not teach the imaging agents recited in claims 2, 3, 6 and 7.

Kayyem et al. teach contrast agent and gene delivery vehicles wherein one of the two polymeric compounds can be a nucleic acid. Kayyem et al. disclose at column 4, lines 1-16 that the contrast agent is one suitable for MRI or PET and includes paramagnetic metals such as iron and gadolinium or radioisotopes such as ^{68}Ga or ^{99}Tc.

The teachings of Kuijpers et al., Priest, Gewirtz et al. and Low et al. are obvious for the reasons set forth in the preceding 103 rejection. It would further have been obvious to one of ordinary skill in the art to substitute the contrast agents taught by Kayyem et al. into the constructs taught by the combination of Kuijpers et al., Priest, Gewirtz et al. and Low et al. because both Kuijpers et al. and Kayyem et al. teach known contrast agents and using those taught by Kayyem et al. would be a matter of simple substitution of known equivalent elements that would reasonably be expected to provide predictable results.

Thus, the invention of claims 1-3, 5-8, 10, 25-27 and 30-32 would have been obvious, as a whole, at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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